Convenient Synthetic Routes to the 5,6-Trimethylenenorbornanones

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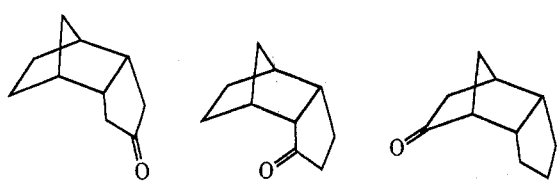
Convenient synthetic routes to the *endo*-5,6-trimethylenenorbornanones, the 8- (II), 9- (I), and 2- (III) ketones, were explored. The selective hydrogenation of *endo*-dicyclopentadiene over nickel boride affords pure *endo*-5,6-trimethylene-8-norbornene. Hydroboration of this olefin, followed by chromic acid oxidation, yields a mixture of I and II, which can be cleanly separated by taking advantage of the finding that I selectively forms a bisulfite addition complex. Oxymercuration–demercuration of *endo*-dicyclopentadiene led to essentially pure 2-alcohol product, the 8- and 9-alcohol products being absent. Hydrogenation of this alcohol, followed by oxidation, gives pure III.

As a part of our studies of the stereoselectivities involved in the reactions of rigid bicyclic and related compounds, we undertook to examine the *endo*-5,6-trimethylenenorbornane system.[3] For this purpose we required relatively large quantities of *endo*-5,6-trimethylene-9-norbornanone (I), *endo*-5,6-trimethylene-8-norbornanone (II), and *endo*-5,6-trimethylene-2-norbornanone (III).[4]



I II III

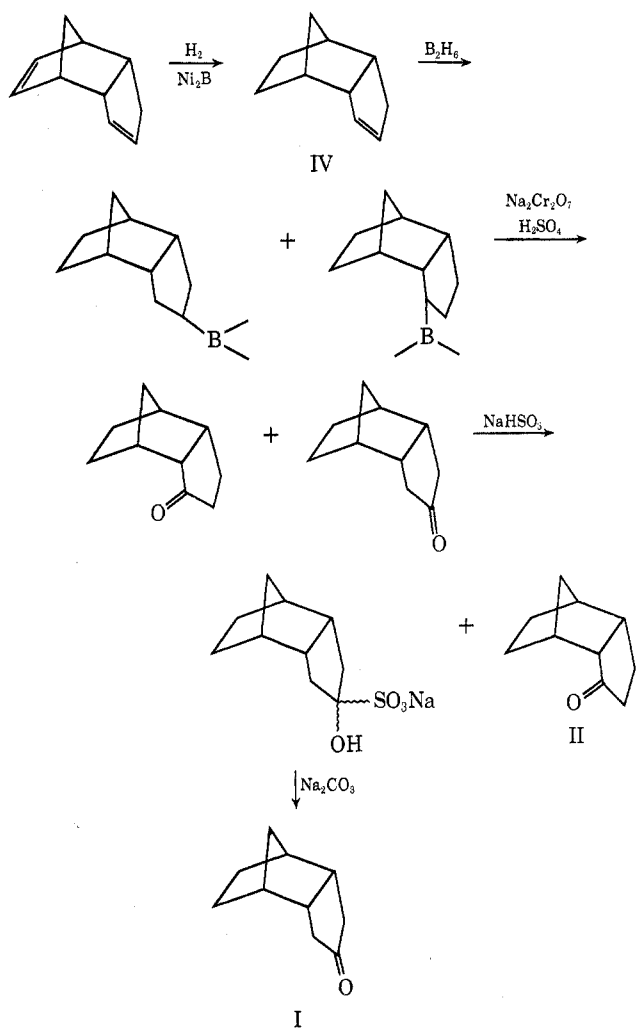
On examining the literature, we found that the synthetic procedures for these ketones are not really satisfactory. The described procedure for I required a number of steps and the yield was not specified.[5] Similarly, the previous methods for preparation of II[6] and III[6,7] involved a number of steps and/or gave poor yields of products of varying purities. Consequently, it was decided to explore more convenient routes to these ketones.

Results and Discussion

endo-5,6-Trimethylene-8-norbornanone (II) and the 9 derivative (I) were prepared by the procedure shown in Scheme I.

Selective hydrogenation of *endo*-dicyclopentadiene in a Brown□ hydrogenator[8] using nickel boride[9,10] as catalyst gave a 90% yield of *endo*-5,6-trimethylene-8-norbornene (IV) of 98.5% purity. Hydroboration[11] of IV followed by chromic acid oxidation of the alkyl boron compounds[12] yielded a 40:60 mixture of I and II. It was found that I quantitatively forms an insoluble bisulfite addition complex, while II is completely unreactive toward sodium bisulfite. The failure of II to form a bisulfite addition complex is probably the result of interference by the endo-3-hydrogen. This is analogous to the behavior of certain steroid ketones, where the angular methyl group also can prevent the formation of bisulfite addition complexes.[13] Similarly, 2,2,4-trimethylcyclopentanone fails to form a bisulfite

SCHEME I



(1) Postdoctorate research associate, 1963–1965.

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(3) H. C. Brown, I. Rothberg, P. v. R. Schleyer, M. M. Donaldson, and J. J. Harper, *Proc. Nat. Acad. Sci. U. S.*, **56**, 1653 (1966); H. C. Brown, I. Rothberg, and D. L. Vander Jagt, *J. Amer. Chem. Soc.*, **89**, 6380 (1967); H. C. Brown, W. J. Hammar, J. H. Kawakami, I. Rothberg, and D. L. Vander Jagt, *ibid.*, **89**, 6381 (1967); H. C. Brown and D. L. Vander Jagt, *ibid.*, **91**, 6850 (1969).

(4) The nomenclature used for this ring system is that used by P. v. R. Schleyer and M. M. Donaldson, *ibid.*, **82**, 4645 (1960).

(5) K. Alder, F. H. Flock, A. Hausweiler, and R. Reefer, *Ber.*, **87**, 1752 (1954).

(6) (a) J. Pirsch, *ibid.*, **67**, 1115 (1935); (b) K. Alder and G. Stein, *Justus Liebigs Ann. Chem.*, **504**, 205 (1933); (c) M. M. Donaldson, Ph.D. Thesis, Princeton University, 1958.

(7) (a) H. Wieland and F. Bergel, *Justus Liebigs Ann. Chem.*, **446**, 13 (1926); (b) S. J. Cristol, W. Steifert, and S. B. Soloway, *J. Amer. Chem. Soc.*, **82**, 235 (1960).

(8) C. A. Brown and H. C. Brown, *J. Org. Chem.*, **31**, 3989 (1966).

(9) H. C. Brown and C. A. Brown, *J. Amer. Chem. Soc.*, **85**, 1004 (1963).

(10) The remarkable effectiveness of this catalyst in performing selective hydrogenation of norbornene double bonds was recently reported: C. A. Brown, *Chem. Commun.*, 952 (1969).

(11) G. Zweifel and H. C. Brown, *Org. React.*, **13**, 1 (1963).

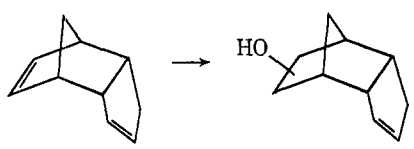
(12) H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.*, **83**, 2951 (1961).

(13) R. L. Clark, *J. Org. Chem.*, **28**, 2626 (1963).

addition complex because of steric repulsions.[14] I and II, thus separated, were found to be better than 98% pure.

In our search for methods of separation of the 8- and 9-ketones, one other facet of investigation appears to be of interest. Owing to the differences in the steric environment of the 8 and 9 positions, it appeared possible that partial oxidation of a mixture of exo-8- and exo-9-alcohols might provide a means of separation through selective oxidation of one isomer. The relative rate of oxidation of the 9-alcohol to the 8-alcohol turned out to be 2.1, which is apparently too small to serve the present purpose. The observation that the oxidation of the exo-9-alcohol is significantly faster than that of the more hindered exo-8-alcohol is puzzling in view of the fact that the more strained alcohols generally undergo more rapid oxidation.[15]

The first step of the synthesis of *endo*-5,6-trimethylene-2-norbornanone (III) involves the conversion of *endo*-dicyclopentadiene to a mixture of 8,9-dehydro and 9,10-dehydro derivatives of *endo*-5,6-trimethylene-*exo*-2-norbornanol (V).

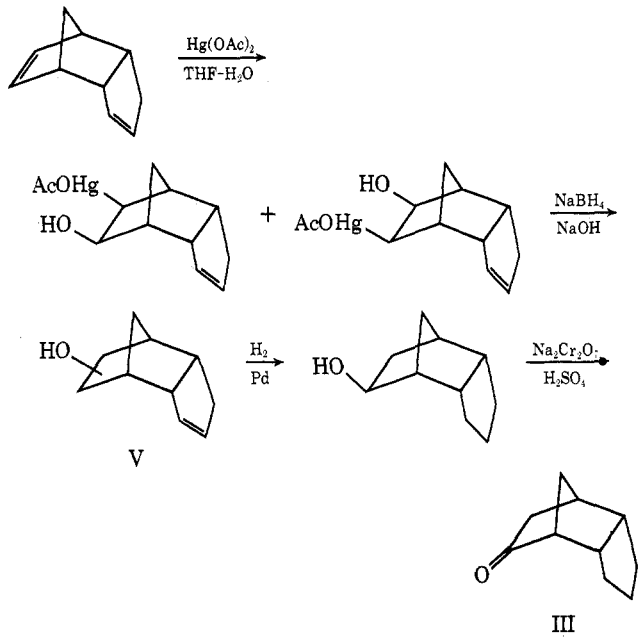


V

We initially utilized hydroboration to achieve this monohydration. However, this reaction was not selective, the product being 37% V and 63% of 8- and 9-hydroxy derivatives. Nevertheless we could quantitatively isolate V from this mixture by extracting ether solutions of the 8- and 9-alcohols with aqueous silver nitrate solution. It was found that *endo*-5,6-trimethylene-2-norbornen-*exo*-8-ol or the 9 derivative readily forms a silver ion complex, while V is essentially unreactive toward silver ion.[16]

It was later found that the above conversion can be carried out cleanly with both high stereospecificity and high yield by means of oxymercuration–demercuration.[19] Treatment of *endo*-dicyclopentadiene with mercuric acetate followed by reduction gave pure V in 89% yield.

Hydrogenation of V was performed according to the previously described procedure using a Brown□ apparatus[8] to obtain *endo*-5,6-trimethylene-*exo*-2-norbornanol in 94% yield. This alcohol was then oxidized utilizing the modified procedure developed in this laboratory[20] to obtain a high yield of pure *endo*-5,6-trimethylene-2-norbornanone (III). The synthetic route to III is summarized below.



V

III

Experimental Section

Glpc Analyses.—All analyses were carried out on a Perkin-Elmer Model 226 with use of a 150 ft × 0.01 in. Golay column coated with Carbowax 20M or UCON LB550X.

***endo*-5,6-Trimethylene-8-norbornene (IV).**—Purified *endo*-dicyclopentadiene (407 g, 3.08 mol) was dissolved in ethanol and submitted to selective hydrogenation in a Brown□ hydrogenator[8] using nickel boride as catalyst.[9,10] After the theoretical amount of hydrogen had been taken up, 200 ml of acetone and 2 g of carbon (Dacro K-B) were added to the reaction mixture and suction filtered through Celite. The solvent was removed and the residue was distilled at atmospheric pressure, bp 178–180°, mp 48.5–50° (lit.[21] mp 50–51°), yield 370 g (90%). Analysis on Ucon LB550X showed 98.5% purity.

***endo*-5,6-Trimethylene-9-norbornanone (I) and *endo*-5,6-Trimethylene-8-norbornanone (II).**—To a well-stirred suspension of 17.0 g (0.450 mol) of sodium borohydride in 500 ml of tetrahydrofuran (THF) containing 134 g (1.0 mol) of *endo*-trimethylene-8-norbornene was added 85.2 g (0.60 mol) of boron trifluoride etherate dissolved in 100 ml of THF over a period of 1 hr under a nitrogen atmosphere. The reaction mixtue was stirred for an additional 2 hr at room temperature and then the excess hydride was decomposed by careful addition of water. A chromic acid solution, prepared from 220 g (0.738 mol) of sodium dichromate dihydrate and 165 ml (2.948 mol) of 96% sulfuric acid and diluted to 1000 ml with water, was added to the stirred solution over a period of 2 hr while the temperature was maintained at 15–20°. The reaction mixture was stirred vigorously for an additional 2 hr at room temperature, and the aqueous phase was separated and washed with two 200-ml portions of ethyl ether. The combined ethereal solution was extracted with three 100-ml portions of saturated sodium carbonate, dried over magnesium sulfate, and condensed to *ca.* 200 ml. Analysis on Carbowax 20M showed the presence of 60% II and 40% I. To this solution 200 ml of ether and 300 ml of saturated aqueous sodium bisulfite were added and the mixture was stirred for 48 hr. Analysis showed that the ethereal solution contained II and I in a ratio of 97:3. The mixture was filtered and the precipitate was washed well with ethyl ether, the washings being added to the filtrate. The ethereal layer of this filtrate was separated, dried over magnesium sulfate, and distilled, affording 52 g (35%) of *endo*-5,6-trimethylene-8-norbornanone (II), bp 132–134° (17

(14) F. G. Gault and J. E. Germain, *Bull. Soc. Chim. Fr.*, 1365 (1959).

(15) For kinetic studies of oxidation of norbornyl and related alcohols, see I. Rothberg and R. V. Russo, *J. Org. Chem.*, **32**, 2003 (1967); I. Rothberg, *Chem. Commun.*, 268 (1968).

(16) The equilibrium constant for the silver ion complex formation of the 8- and 9-alcohols in the present system, $K = [\text{complex}]_{H_2O}/[Ag^+]_{H_2O}[\text{Olefin}]_{\text{ether}}$ was found to be 10 l./mol at 25°. Previous studies in this area showed that norbornene forms a silver ion complex more readily than cyclopentene, but the difference was found to be small.[17] The difference observed for the compounds under consideration is large enough to enable a quantitative separation. This may be due either to changes in structural variations, such as changes in bond angles caused by the introduction of the trimethylene bridge[18] or to differences in solubility in the aqueous phase.

(17) J. G. Traynham and M. F. Sehnert, *J. Amer. Chem. Soc.*, **78**, 4024 (1956); J. G. Traynham and J. R. Olechowski, *ibid.*, **81**, 571 (1959).

(18) It is known that introduction of substituents induces distortion of the norbornane structure: C. Altona and M. Sundaralingam, *ibid.*, **92**, 1995 (1970).

(19) H. C. Brown and P. Geoghegan, *ibid.*, **89**, 1522 (1967).

(20) H. C. Brown, C. P. Garg, and K.-T. Liu, *J. Org. Chem.*, **36**, 387 (1971); H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.*, **83**, 2952 (1961).

(21) K. Alder and G. Stein, *Justus Liebigs Ann. Chem.*, **485**, 223 (1931).

mm), mp 94–97°. Analysis showed 95% purity, 2% being I and 3% lower boiling unidentified materials. Recrystallization from pentane gave mp 98–99° (lit.[7a] mp 101°), semicarbazone mp 200–201° (lit.[7a] mp 200°). The precipitate, which had been set aside, was added to a mixture of 300 ml of saturated aqueous sodium carbonate and 200 ml of ethyl ether and stirred vigorously until solution had occurred. The ether layer was separated and the aqueous carbonate layer was extracted with two 50-ml ether portions. The ether portions were combined, dried over magnesium sulfate, and distilled to yield 42 g (28%) of *endo*-5,6-trimethylene-9-norbornanone (I), bp 132–134° (20 mm), mp 105–105.5°, semicarbazone mp 214–215°, dibenzylidene derivative mp 191–191.5° (lit.[6] semicarbazone mp 215°, dibenzylidene derivative mp 191°). *Anal.* Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 80.16; H, 9.57.

Relative Rates of Oxidation of *endo*-5,6-Trimethylene-*exo*-9-norbornanol and the Exo-8 Isomer.—A mixture of alcohols consisting of 9.75 mmol of *endo*-5,6-trimethylene-*exo*-9-norbornanol and 15.25 mmol of *endo*-5,6-trimethylene-*exo*-8-norbornanol, obtained by hydroboration of *endo*-5,6-trimethylene-8-norbornene, was treated wth 50% of the theoretical amount of chromic acid using the previously described procedure.[20] At the end of the reaction glpc analysis revealed that there remained 3.85 mmol of the 9-alcohol and 9.90 mmol of the 8-alcohol. According to the given procedure,[22] the rate of oxidation of the 9-alcohol relative to that of the 8 isomer was calculated to be 2.1.

8,9-Dehydro- and 9,10-Dehydro-*endo*-5,6-trimethylene-*exo*-2-norbornanol (V). Method A. Hydroboration of *endo*-Dicyclopentadiene.—To a well-stirred solution containing 198 g (1.5 mol) of *endo*-dicyclopentadiene in 250 ml of THF was added under a nitrogen atmosphere 167 ml (1 mol of hydride) of 1 *M* diborane solution in THF. The solution was allowed to become hot owing to an exothermic reaction. After addition was complete, the reaction mixture was stirred for 3 hr, and then 150 ml of 3 *N* sodium hydroxide was added, followed by the slow addition of 150 ml of 30% hydrogen peroxide, and stirred for 8 hr. The THF layer was salted out by adding potassium carbonate and separated. The aqueous phase was extracted with ether and the combined solution was dried over magnesium sulfate before the solvent was distilled off. The residue was distilled to give 72 g (0.55 mol) of the starting material, bp 70–75° (18 mm), 96 g (0.64 mol) of a mixture of monoalcohols, bp 124–130° (15 mm), and higher boiling diols. Analysis of the monoalcohol showed the presence of 37% 2-alcohol (V). A 1 *M* ether solution of this mixture of monoalcohols was extracted three times with a 1 *M* silver nitrate solution using $^2/_3$ the volume of silver nitrate each time as the total volume of ether solution. The aqueous portions were extracted once with ether and then back extracted once with silver nitrate solution. The combined ether solution was washed once with water and then dried over magnesium sulfate. The ether was distilled off at a reduced pressure to give a quantitative recovery of V.

Method B. Oxymercuration–Demercuration[19] of *endo*-Dicyclopentadiene.—Mercuric acetate (63.7 g, 0.2 mol) was dissolved in 200 ml of water and 200 ml of THF, and to the resulting yellow solution was added with stirring 26.4 g (0.2 mol) of *endo*-dicyclopentadiene. After the yellow color disappeared the mixture was stirred for an additional 10 min and cooled to *ca.* −10°. To this solution was added successively 200 ml of cold 3 *N* sodium hydroxide solution and 200 ml of cold basic sodium borohydride solution (0.5 *M* in borohydride and 3 *N* in sodium hydroxide). The mixture was stirred until mercury settled and the aqueous layer was separated and extracted with hexane. The combined organic solution was dried over magnesium sulfate and the solvent was removed under a reduced pressure. Analysis showed the presence of 91% alcohol and 9% acetate. The residue was then treated with lithium aluminum hydride in THF in order to reduce the small amount of acetate and, at the same time, to reduce any residual mercurial products which were found to interfere with the catalytic hydrogenation. The final product was isolated in the usual manner. Analysis showed that the reaction proceeded to the extent of 89.5%, the product being practically pure 2-alcohol (V).

***endo*-5,6-Trimethylene-*exo*-2-norbornanol.**—The mixture of 8,9-dehydro- and 9,10-dehydro-*endo*-5,6-trimethylene-*exo*-2-norbornanol (V) was reduced according to the previous procedure.[8] The product was recrystallized from pentane, mp 81.5–82.0° (lit.[7b] mp 80.5–81.5°).

***endo*-5,6-Trimethylene-2-norbornanone (III).**—*endo*-5,6-Trimethylene-*exo*-2-norbornanol was oxidized with use of the modified procedure developed in this laboratory.[20] The crude product, obtained in 95% yield, was essentially free of the starting material as shown by glpc analysis. The product was purified by sublimation, mp 102–104° (lit.[7b] mp 97–103°).

Registry No.—I, 19138-60-4; 8,9-dehydro-V, 36807-74-6; 9,10-dehydro-V, 36807-75-7; *endo*-dicyclopentadiene, 1755-01-7.

(22) R. Stewart, "Oxidation Mechanisms," W. A. Benjamin, New York' N. Y., 1964, p 39.

Effects of Substituents on the Rates of Disproportionation of Substituted Phenylglyoxals in Alkaline Solution[1a,b]

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A series of meta- or para-substituted phenylglyoxals, including H, *p*-CH_3, *p*-OCH_3, *p*-Br, *p*-Cl, *p*-phenyl, *m*-OCH_3, *p*-NO_2, and *p*-OH, were examined for linear free energy relationships between chemical reactivity and substituent constants, and between chemical reactivity and carbonyl stretching frequencies of the ketone and aldehyde carbonyls. At pH 12, the hydroxide ion catalyzed disproportionation of the phenylglyoxals into the corresponding mandelic acids follows the Hammett relationship with ρ 2.0, indicative of a transition state stabilized by electron-withdrawing groups. These rates of disproportionation also correlate quite well with the carbonyl stretching frequencies of the ketone carbonyls, both for the hydrated and the anhydrous phenylglyoxals. The aldehyde carbonyl stretching frequencies are essentially independent of ring substituents, $\nu_{C=O}$ 1727 ± 2 cm^{-1}. The disproportionation of α-keto aldehydes is known to involve intramolecular hydride migration. The results of the present study suggest that hydride migration is the rate-determining step in the disproportionation of this series of substituted phenylglyoxals.

The glyoxalase system is composed of two enzymes: glyoxalase I, which utilizes glutathione (GSH) as co-enzyme and catalyzes the disproportionation of methylglyoxal into the thiol ester of lactic acid and GSH, and glyoxalase II, which hydrolyzes this thiol ester to regenerate GSH and liberate lactic acid.[2,3] Scheme I

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(2) E. Racker, *J. Biol. Chem.*, **190**, 685 (1951).

(3) Review article on glutathione and the glyoxalase system: W. E. Knox in "The Enzymes," Vol. 2, P. D. Boyer, H. Lardy, and K. Myrback, Ed., Academic Press, New York, N. Y., 1960, p 253.